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L1: Entry 56 of 83 File: USPT Jan 13, 1998

US-PAT-NO: 5707608
DOCUMENT-IDENTIFIER: US 5707608 A

TITLE: Methods of making liposomes containing hydro-monobenzoporphyrin photosensitizer

DATE-ISSUED: January 13, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 424/9.61; 424/9.1, 424/9.6

CLAIMS:

We claim:

1. A method for making a pharmaceutical composition containing liposomes, said liposomes comprising a therapeutically acceptable amount of a hydro-monobenzoporphyrin photosensitizer and a mixture of phospholipids comprising egg phosphatidyl glycerol ("EPG") and dimyristoyl phosphatidyl choline ("DMPC"), wherein said method comprises the steps of:

a. combining the photosensitizer and the phospholipids in a molar ratio of 1:7.0 or more phospholipid in the presence of an organic solvent;

b. removing said organic solvent to form a photosensitizer:phospholipid complex;

c. hydrating said photosensitizer:phospholipid complex with an aqueous solution at a temperature below the glass transition temperature of the photosensitizer:phospholipid complex to form coarse liposomes containing said photosensitizer-phospholipid complex; and

d. homogenizing or reducing the particle size of said coarse liposomes to a particle size range of below about 300 nm at a temperature below the glass transition temperature of the photosensitizer:phospholipid complex.

2. The method of claim 1, wherein said molar ratio of hydro-monobenzoporphyrin photosensitizer to phospholipids is about 1:8.0 or more phospholipid.

3. The method of claim 1, wherein said organic solvent is methylene chloride.

4. The method of claim 1, wherein said organic solvent is removed in step "b." by evaporation under reduced pressure.

5. The method of claim 1, wherein said aqueous solution comprises a disaccharide or polysaccharide.

6. The method of claim 4, wherein said disaccharide or polysaccharide is selected from lactose or trehalose.

7. The method of claim 4, wherein the concentration ratio of disaccharide or polysaccharide to said mixture of phospholipids is about 10-20 to 0.5-6.0.

8. The method of claim 1, wherein said hydro-monobenzoporphyrin (Gp) photosensitizer has one of the formulae 1-6 set forth in FIG. 1 and has one or more light absorption maxima between 670-780 nm, or is a metalated or labeled form thereof,

wherein

each R.sup.1 and R.sup.2 is independently selected from the group consisting of carbalkoxy (2-6C), alkyl (1-6C) sulfonyl, aryl (6-10C) sulfonyl, aryl (6-10C), cyano, and --CONR.sup.5 CO-- wherein R.sup.5 is aryl (6-10C) or alkyl (1-6C);

each R.sup.3 is independently carboxyalkyl (2-6C) or a salt, amide, ester or acylhydrazone thereof, or is alkyl (1-6C); and

R.sup.4 is --CHCH.sub.2 ; --CHOR.sup.4' wherein R.sup.4' is H or alkyl (1-6C), optionally substituted with a hydrophilic substituent; --CHO; --COOR.sup.4' ; --CH(OR.sup.4')CH.sub.3 ; --CH(OR.sup.4')CH.sub.2 OR.sup.4' ; --CH(SR.sup.4')CH.sub.3 ; --CH(NR.sup.4'.sub.2)CH.sub.3 ; --CH(CN)CH.sub.3 ; --CH(COOR.sup.4')CH.sub.3 ; --CH(OOCR.sup.4')CH.sub.3 ; --CH(halo) CH.sub.3 ; --CH(halo)CH.sub.2 (halo); an organic group of less than 12C resulting from direct or indirect derivatization of a vinyl group; or R.sup.4 is a 1-3 tetrapyrrole-type nucleus of the formula --L--P, wherein --L-- is selected from the group consisting of ##STR3## and P is a second Gp, which is one of the formulae 1-6 but lacks R.sup.4 and is conjugated to L through the position shown as occupied by R.sup.4, or another porphyrin group.

9. The method of claim 8 wherein, when P is said another porphyrin group, P has the formula: ##STR4## wherein: each R is independently H or lower alkyl (1-4C);

two of the four bonds shown as unoccupied on adjacent rings are joined to R.sup.3 ;

one of the remaining bonds shown as unoccupied is joined to R.sup.4 ; and

the other is joined to L;

with the proviso that, if R.sup.4 is CHCH.sub.2, said R.sup.3 groups cannot both be carbalkoxyethyl.

10. The method of claim 8, wherein each R.sup.3 is --CH.sub.2 CH.sub.2 COOH or salt, amide, ester or acylhydrazone thereof.

11. The method of claim 8, wherein each of R.sup.1 and R.sup.2 is carbalkoxy (2-6C).

12. The method of claim 1, wherein the photosensitizer is BPD-MA having the formula of FIG. 2.

13. The method of claim 1, wherein said hydrating step "c." is accomplished at a temperature at or below room temperature.

14. The method of claim 1, wherein said homogenizing or reducing step "d." is accomplished at a temperature at or below room temperature.

15. The method of claim 1, wherein said particle size is reduced to a range of below about 250 nm.

16. The method of claim 15 wherein the particle size is reduced to below about 220 nm.

17. A pharmaceutical composition containing liposomes in the particle size range of about 150 to 300 nm, wherein said liposomes comprise:

a. a therapeutically acceptable amount of a photosensitizer and

b. a mixture of phospholipids comprising:

(1) egg phosphatidyl glycerol ("EPG") and

(2) dimyristoyl phosphatidyl choline ("DMPC"),

wherein the molar ratio of said photosensitizer and said mixture of phospholipids is about 1:7.0 or more phospholipid.

18. The composition of claim 17, wherein said molar ratio of photosensitizer to said mixture of phospholipids is about 1:8.0 or more phospholipid.

19. The composition of claim 17, wherein said hydro-monobenzoporphyrin (Gp) has one of the formulae 1-6 set forth in FIG. 1 and has one or more light absorption maxima between 670-780 nm, or is a metalated or labeled form thereof, wherein:

each R.sup.1 and R.sup.2 is independently selected from the group consisting of carbalkoxy (2-6C), alkyl (1-6C) sulfonyl, aryl (6-10C) sulfonyl, aryl (6-10C), cyano, and --CONR.sup.5 CO-- wherein R.sup.5 is aryl (6-10C) or alkyl (1-6C);

each R.sup.3 is independently carboxyalkyl (2-6C) or a salt, amide, ester or acylhydrazone thereof, or is alkyl (1-6C); and

R.sup.4 is --CHCH.sub.2 ; --CHOR.sup.4' wherein R.sup.4' is H or alkyl (1-6C), optionally substituted with a hydrophilic substituent; --CHO; --COOR.sup.4' ; --CH(OR.sup.4'.sub.2) CH.sub.3 ; --CH(OR.sup.4')CH.sub.2 OR.sup.4' ; --CH(SR.sup.4')CH.sub.3 ; --CH(NR.sup.4') CH.sub.3 ; --CH(CN)CH.sub.3 ; --CH(COOR.sup.4')CH.sub.3 ; --CH(OOCR.sup.4')CH.sub.3 ; --CH(halo)CH.sub.3 ; --CH(halo)CH.sub.2 (halo); an organic group of less than 12C resulting from direct or indirect derivatization of a vinyl group; or R.sup.4 is a 1-3 tetrapyrrole-type nucleus of the formula --L--P, wherein --L-- is selected from the group consisting of ##STR5## and P is a

second Gp, which is one of the formulae 1-6 but lacks R.sup.4 and is conjugated to L through the position shown as occupied by R.sup.4, or another porphyrin group.

20. The composition of claim 19 wherein, when P is said another porphyrin group, it has the formula: ##STR6## wherein each R is independently H or lower alkyl (1-4C);

two of the four bonds shown as unoccupied on adjacent rings are joined to R.sup.3 ;

one of the remaining bonds shown as unoccupied is joined to R.sup.4 ; and

the other is joined to L;

with the proviso that, if R.sup.4 is CHCH.sub.2, said R.sup.3 groups cannot both be carbalkoxyethyl.

21. The composition of claim 20, wherein each R.sup.3 is --CH.sub.2 CH.sub.2 COOH or a salt, amide, ester or acylhydrazone thereof.

22. The composition of claim 19, wherein each of R.sup.1 and R.sup.2 is carbalkoxy (2-6C).

23. The composition of claim 19, wherein the hydro-monobenzoporphyrin photosensitizer is BPD-MA having the formula of FIG. 2.

24. The composition of claim 19, wherein said particle size is below about 220 nm.

L1: Entry 73 of 83 File: USPT Oct 1, 1991

DOCUMENT-IDENTIFIER: US 5053423 A
TITLE: Compositions for photodynamic therapy

Brief Summary Text (9):
The use of liposomes or lipoproteins as pharmaceutical excipients for hematoporphyrins and related compounds has also been described. In addition, conventional pharmaceutical excipients have been used; however, the ability to administer significant amounts of photosensitizing drug in a relatively small volume of composition is impaired by the intrinsic water insolubility of most of these compounds. The present invention provides a means to solubilize these photosensitizers in a manner which permits ready administration while having no adverse effects on the accumulation on these materials in target cells or viruses or on the ability of the photosensitizing agent to absorb the appropriate radiation and exert cytotoxic effects or be detectable by fluorescence.